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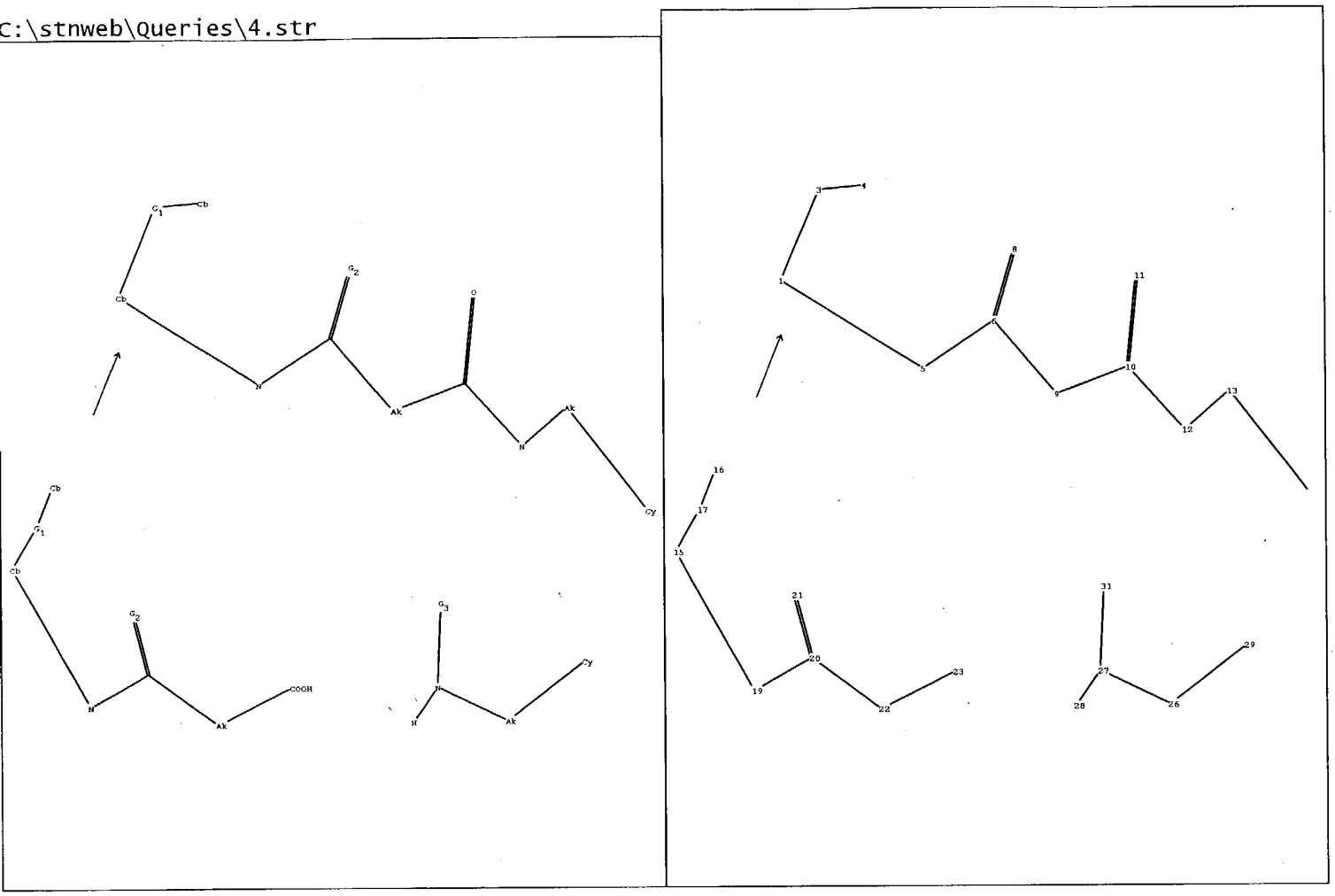

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31
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1-3 1-5 3-4 5-6 6-8 6-9 9-10 10-11 10-12 12-13 13-14 15-17 15-19 16-17
19-20 20-21 20-22 22-23 26-27 26-29 27-28 27-31
exact/norm bonds :
1-3 3-4 5-6 6-8 6-9 9-10 10-11 10-12 12-13 13-14 15-17 16-17 19-20 20-21
20-22 22-23 26-27 26-29 27-31
exact bonds :
1-5 15-19 27-28

G1:O,S

G2:H,O,S

G3:H,Ak

Match level :
1:Atom 3:CLASS 4:Atom 5:CLASS 6:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS
13:CLASS 14:Atom 15:Atom 16:Atom 17:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS
23:CLASS 26:CLASS 27:CLASS 28:CLASS 29:Atom 31:CLASS
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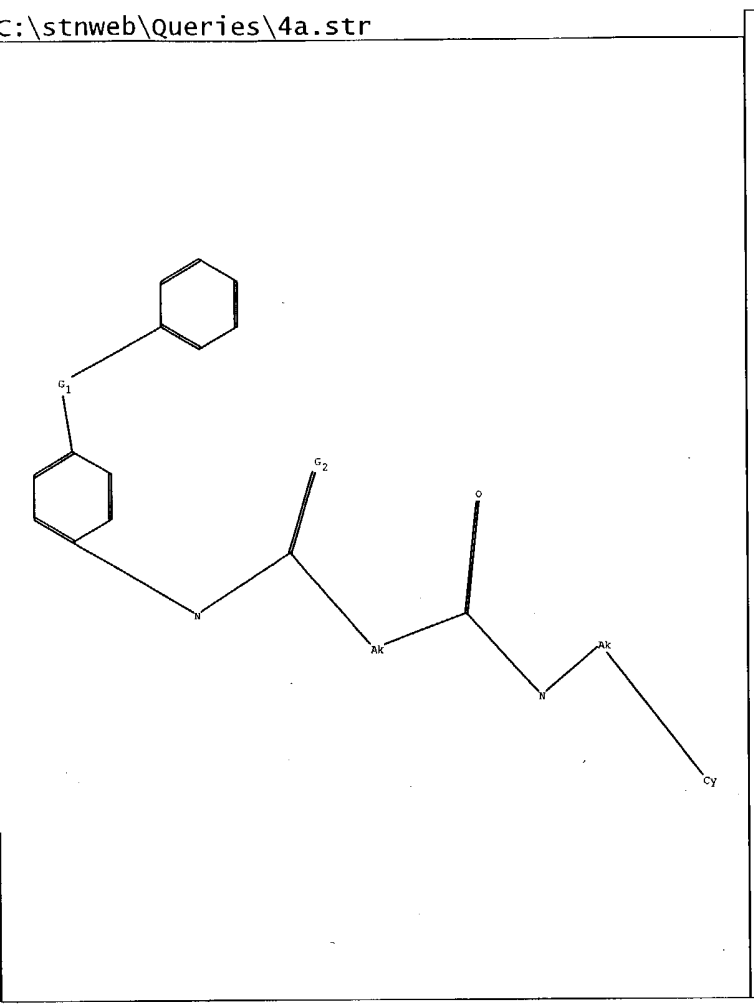

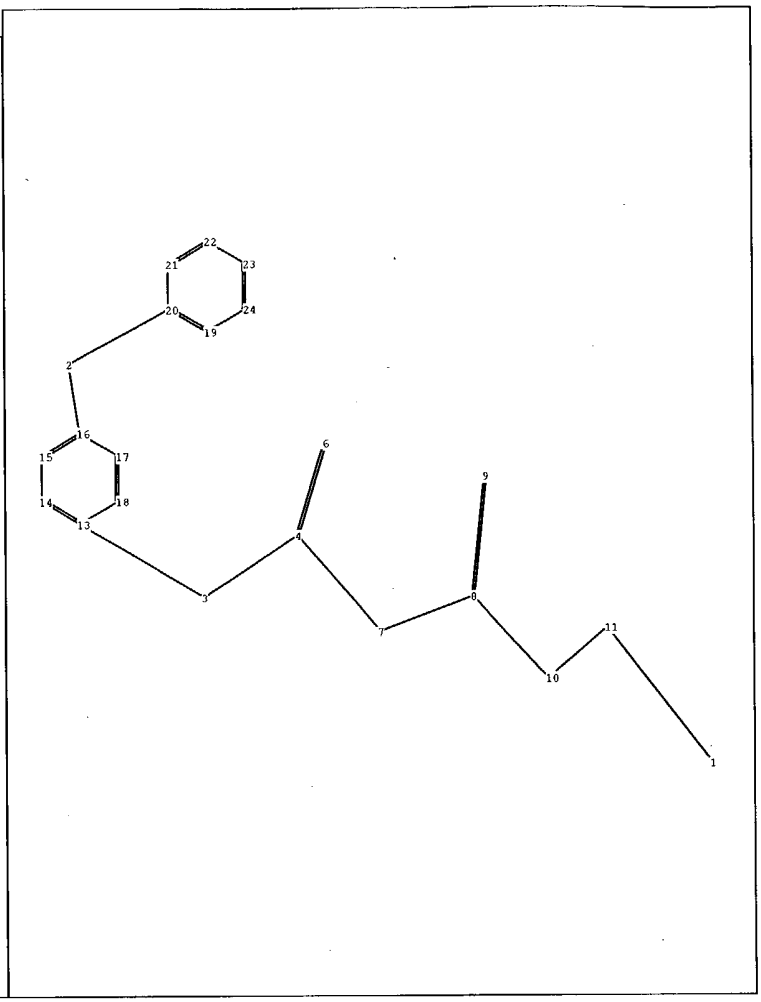

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13-14 13-18 14-15 15-16 16-17 17-18 19-20 19-24 20-21 21-22 22-23 23-24
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normalized bonds :
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G1:O,S

G2:H,O,S

Match level :
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22:Atom 23:Atom 24:Atom

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     (FILE 'HOME' ENTERED AT 13:34:26 ON 17 NOV 2004)

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L1       3058928 S SOMATOSTATIN OR SST OR RECEPTOR? OR SUBTYPE?
L2       5075530 S ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR
L3       1349552 S L1 AND L2
L4         94956 S SOMATOSTATIN OR SST
L5         26064 S L4 AND L2
L6       5979652 S ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR
L7         38217 S L6 AND L4
L8        173209 S DIARRHEA? OR INTRACTABLE () DIARRHEA?
L9          1037 S L8 AND L7
L10          197 S L9 AND REVIEW
L11         9308 S DIABETIC? () COMPLICATION?
L12           24 S L11 AND L7
L13            6 S L12 AND REVIEW
L14       220858 S OBESITY
L15          410 S L14 AND L7
L16           65 S L15 AND REVIEW
L17         1699 S OL, S?/AU
L18        14125 S SUZUKI, N?/AU
L19         1315 S ASO, K?/AU
L20          787 S BANNO, Y?/AU
L21            0 S L17 AND L18 AND L19 AND 120
L22            0 S L17 AND L18

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                    fields
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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
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                                                       ENTRY    SESSION
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=> s somatostatin or SST or receptor? or subtype?
L1      3058928 SOMATOSTATIN OR SST OR RECEPTOR? OR SUBTYPE?

=> s ?agonist? or ligand? or inhibitor? or modulator? or regulator?
L2      5075530 ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR?

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L3      1349552 L1 AND L2

=> s somatostatin or sst
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=> s l4 and l2
L5        26064 L4 AND L2

=> s ?agonist? or ligand? or inhibitor? or modulator? or regulator? or analog?
L6      5979652 ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR?
                OR ANALOG?

=> s l6 and l4
L7        38217 L6 AND L4

=> s diarrhea? or intractable () diarrhea?
L8       173209 DIARRHEA? OR INTRACTABLE (W) DIARRHEA?

=> s l8 and l7
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=> s l9 and review
L10         197 L9 AND REVIEW

=> d 1-10 cbib abs

L10  ANSWER 1 OF 197     MEDLINE on STN
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1998353028. PubMed ID: 9690718. **Review** article: colonic sensorimotor physiology in health, and its alteration in constipation and diarrhoeal disorders. Camilleri M; Ford M J. (Mayo Medical School, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.) Alimentary pharmacology & therapeutics, (1998 Apr) 12 (4) 287-302. Ref: 135. Journal code: 8707234. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom. Language: English.

AB AIM: To **review** the physiology of colonic motility and sensation in healthy humans and the pathophysiological changes associated with constipation and diarrhoea. SOURCE: Medline Search from 1965 using the index terms: human, colonic motility, sensation, pharmacology, neurohormonal control, gastrointestinal transit, constipation, diarrhoea and combinations of these. RESULTS: In health, the ascending and transverse regions of colon function as reservoirs to accommodate ileal chyme and the descending colon acts as a conduit; the neuromuscular functions and transmitters control colonic motility and sensation and play pivotal roles in disorders associated with constipation and/or diarrhoea. Disorders of proximal colonic transit contribute to symptoms in idiopathic constipation, diarrhoea-predominant irritable bowel syndrome and carcinoid diarrhoea. Colonic function in patients presenting with constipation is

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best assessed clinically by colonic transit time using radiopaque markers ingested orally. Measurements of colonic contractility are less useful clinically but they can help identify motor abnormalities including colonic inertia; in some patients with irritable bowel syndrome, abdominal pain, urgency and diarrhoea are temporally associated with high amplitude contractions, which originate in the proximal colon and traverse the distal conduit at very high propagation velocities. Visceral hypersensitivity contributes to the urgency and tenesmus in irritable bowel syndrome and inflammatory bowel disease. Colonic motility and sensation can be reduced by anticholinergic agents, **somatostatin analogues** and 5HT3 **antagonists**. CONCLUSION: Physiological and pharmacological studies of the human colon have provided new insights into the pathophysiology of colonic disorders, and offer possibilities of novel therapeutic approaches for constipation or diarrhoea associated with colonic motor or sensory dysfunction.

L10 ANSWER 2 OF 197 MEDLINE on STN

Citing References

95329561. PubMed ID: 7605866. **Review** article: anti-diarrhoeal pharmacology and therapeutics. Schiller L R. (Gastrointestinal Physiology Laboratory, Baylor University Medical Center, Dallas, TX 75246, USA.) Alimentary pharmacology & therapeutics, (1995 Apr) 9 (2) 87-106. Ref: 271. Journal code: 8707234. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Anti-diarrhoeal drugs reduce the symptoms of diarrhoea (loose stool consistency, frequency of defecation and excessive stool weight) by effects on intestinal transit, mucosal transport or luminal contents. Opiates and opioids are the most useful antidiarrhoeal agents. Opiates have major effects on intestinal transit; pro-absorptive and anti-secretory effects are less well documented, but may be important for some of these drugs. Alpha-adrenergic **agonists**, **somatostatin analogues** and several other agents have had limited clinical use; these drugs may modify mucosal transport in addition to slowing transit. Adsorbents, bismuth and stool texture modifiers are used frequently by the public, but their efficacy is largely unproven. Oral rehydration solutions have had the greatest impact in saving lives and continue to be improved. Many new approaches to the treatment of diarrhoea are yet to be exploited.

L10 ANSWER 3 OF 197 MEDLINE on STN

Citing References

95210456. PubMed ID: 7696444. **Review** article: practical management of the short bowel. Lennard-Jones J E. (St Mark's Hospital, London, UK.) Alimentary pharmacology & therapeutics, (1994 Dec) 8 (6) 563-77. Ref: 91. Journal code: 8707234. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A shortened small intestine may end at a stoma or be anastomosed to the colon. Patients with a jejunostomy, but not those with a colon, lose large amounts of sodium. The intake and absorption of sodium can be increased by sipping a sodium-glucose solution; stomal loss can be reduced by restricting water or low-sodium drinks. If a stoma is situated less than 100 cm along the jejunum, a constant negative sodium balance may necessitate parenteral saline supplements. Gastric anti-secretory drugs or a **somatostatin analogue** reduce jejunostomy losses in such patients but do not restore a positive sodium balance. Loperamide or codeine phosphate benefit some patients. Magnesium deficiency can usually be corrected by oral magnesium oxide supplements. An elemental or hydrolysed diet is not beneficial. Patients with a jejunostomy can maintain a normal

diet without fat reduction. When the colon is present, unabsorbed carbohydrate is fermented to absorbable short chain fatty acids. Unabsorbed long chain fatty acids and bile salts cause watery diarrhoea and increased colonic oxalate absorption with hyperoxaluria. Such patients benefit from a high carbohydrate, low-fat and low-oxalate diet. Parenteral nutrition is needed only by the few patients unable to maintain health or avoid socially disabling diarrhoea despite these measures.

L10 ANSWER 4 OF 197 MEDLINE on STN

Links References

95038247. PubMed ID: 7950821. Liver VIPoma: report of two cases and literature **review**. Lundstedt C; Linjawi T; Amin T. (Department of Radiology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudia Arabia.) Abdominal imaging, (1994 Sep-Oct) 19 (5) 433-7. Ref: 29. Journal code: 9303672. ISSN: 0942-8925. Pub. country: United States. Language: English.

AB Two cases of neuroendocrine tumor in the liver, positive for VIP, without evidence of a primary tumor outside the liver is presented. One patient had a VIPoma syndrome with **diarrhea**, hypokalemia, and hypercalcemia, all symptoms were reversible after treatment consisting of **somatostatin analogue** and arterial liver embolization followed by liver resection. The other patient showed no endocrine symptoms. To the best of our knowledge, VIPomas apparently primary in the liver have not been previously described.

L10 ANSWER 5 OF 197 MEDLINE on STN

Links References

94908249. PubMed ID: 10150156. Pharmacoeconomics of the therapy of diarrhoeal disease. Nathavitharana K A; Booth I W. (Institute of Child Health, University of Birmingham, Edgbaston, England.) PharmacoEconomics, (1992 Oct) 2 (4) 305-23. Ref: 138. Journal code: 9212404. ISSN: 1170-7690. Pub. country: New Zealand. Language: English.

AB We **review** the pathophysiology of intestinal water and electrolyte transport leading to diarrhoea, the currently available pharmacological strategies for its treatment, and the economic implications of such treatments. Diarrhoea occurs most frequently and is associated with highest mortality in children under 5. Oral rehydration therapy (ORT) is the cornerstone of its management. The safety and efficacy of ORT in the prevention of death from dehydration, both in field and also in hospital settings, are now well established. Because it is also inexpensive, ORT is widely applicable worldwide. More recently, rice-based ORT has emerged, based on well known traditional remedies for diarrhoea in southeast Asia and the Far East. Rice-based ORT has the advantage of being more culturally acceptable, readily available even in rural homes in developing countries, and is more effective in reducing stool output and the duration of diarrhoea, compared with conventional glucose-electrolyte solutions such as World Health Organization ORT. For infants, the well known antidiarrhoeal properties of human milk needs emphasis for a variety of reasons including economic ones. Data concerning the economic benefits to a nations' health budget as a result of nationwide implementation of oral rehydration solution (ORS) use are limited. Available data from individual centres in developing countries, if projected to national level, would incur considerable economic advantage. Except for a few notable infections such as shigellosis, cholera, amoebiasis and giardiasis, the widespread use of antibiotics in acute diarrhoea, still a common practice in many developing countries, has no proven value and may be detrimental. The economic implications of antibiotic abuse in the treatment of diarrhoea in developing countries is enormous. Despite the

availability of a wide spectrum of pharmacological agents for diarrhoea reviewed in this article, only a few such agents are of proven clinical efficacy: corticosteroids, aminosalicylates and immunosuppressants in the treatment of inflammatory bowel disease and opioid derivatives such as loperamide which may be useful in protracted diarrhoea in children and in disorders where rapid gastrointestinal transit is the main cause of diarrhoea. Opioids are not recommended for acute infective diarrhoea in childhood. Octreotide, a **somatostatin analogue**, is reported to be useful in the treatment of secretory diarrhoea due to noninfective causes and in the treatment of intractable diarrhoea associated with AIDS. Its high cost and need for parenteral administration prevent its wider application.(ABSTRACT TRUNCATED AT 400 WORDS)

L10 ANSWER 6 OF 197 MEDLINE on STN

Citing References

91254430. PubMed ID: 1675056. Updates on AIDS cryptosporidiosis: a **review**. Garrido Davila J I; Ramirez Ronda C H. (Infectious Diseases Program, University of Puerto Rico School of Medicine, San Juan DVA.) Boletin de la Asociacion Medica de Puerto Rico, (1991 Feb) 83 (2) 65-8. Ref: 15. Journal code: 7505267. ISSN: 0004-4849. Pub. country: Puerto Rico. Language: English.

AB Cryptosporidium is a protozoal coccidian parasite that produces among other diseases chronic watery **diarrhea**. The extent of the diseases is mostly dependent on the immune status of the individual. Mortality in immunosuppressed and AIDS individuals due to the **diarrhea** illness is nearly 80%. Although no effective treatment is available yet, promising results have been related to the use of Spiramycin, Erythromycin, **Somatostatin** and its **analogues**, and zidovudine.

L10 ANSWER 7 OF 197 MEDLINE on STN

Citing References

91020586. PubMed ID: 2219445. Endocrine diarrhoeas: current concepts. Misra S C. (Department of Gastroenterology, AIIMS, New Delhi, India.) Tropical gastroenterology : official journal of the Digestive Diseases Foundation, (1990 Apr-Jun) 11 (2) 87-98. Ref: 50. Journal code: 8107122. ISSN: 0250-636X. Pub. country: India. Language: English.

AB Chronic diarrhoea occurs in several endocrine gland disorders, largely in gut neuro-endocrine tumours, due to the release of various agents into circulation, which affect gastrointestinal function (Table I). In the strict physiological sense, these agents may be hormones (such as gastrin), paracrine substance (**somatostatin**), neurotransmitters or neuro **modulators** (vasoactive intestinal polypeptide; VIP) or unknown agent(s) yet to be identified. For each of these syndromes or diseases (Table I), this **review** considers the characteristics of diarrhoea, its pathogenesis and the therapeutic aspects. The approach to the diagnosis of these syndromes, including localization of tumour tissue and the selection of appropriate anti-tumor treatment are also outlined.

L10 ANSWER 8 OF 197 MEDLINE on STN

Citing References

90343907. PubMed ID: 2200414. New drug treatment for diarrhoea. Donowitz M; Levine S; Watson A. (Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.) Journal of internal medicine. Supplement, (1990) 732 155-63. Ref: 38. Journal code: 8912975. ISSN: 0955-7873. Pub. country: ENGLAND: United Kingdom. Language: English.

AB This paper **reviews** the scientific background to the development of new drugs for the treatment of diarrhoeal diseases, and it includes an update

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of three classes of drugs which may prove useful; gut specific alpha2-adrenergic **agonists**, intestinal Cl- channel blockers, and **somatostatin analogues**.

L10 ANSWER 9 OF 197 MEDLINE on STN

90125617. PubMed ID: 2558839. Debut of a **somatostatin analog**: octreotide in **review**. Zindel L R. Connecticut medicine, (1989 Dec) 53 (12) 741-4. Ref: 16. Journal code: 0372745. ISSN: 0010-6178. Pub. country: United States. Language: English.

AB Octreotide is a long-acting cyclic octapeptide with pharmacologic actions mimicking those of the natural hormone **somatostatin**. It can suppress the secretion of serotonin, as well as the gastroenteropancreatic peptides gastrin, vasoactive intestinal peptide (VIP), insulin, glucagon, secretin, motilin, and pancreatic polypeptide. It also suppresses growth hormone and decreases splanchnic blood flow. Octreotide is completely and rapidly absorbed following subcutaneous injection and has an elimination half-life of 1.5 hours. Clinical trials reviewed here show octreotide useful in the treatment of **diarrhea** associated with VIP secreting tumors, as well as **diarrhea** and flushing associated with carcinoid syndrome, both conditions for which the drug is approved. Clinical trials involving the use of octreotide in the treatment of acromegaly are also reviewed. Adverse reactions to octreotide are mild to moderate and most commonly involve injection site pain and **diarrhea**. Drug interactions are apparently related to the drug's pharmacologic effects. Octreotide is given subcutaneously two to three times daily, with daily doses ranging from 50mcg to 1,500mcg per day. Further research appears necessary to clarify dosing issues.

L10 ANSWER 10 OF 197 MEDLINE on STN

89302765. PubMed ID: 2663049. Clinical features of carcinoid syndrome and the use of **somatostatin analogue** in its management. Vinik A I; Thompson N; Eckhauser F; Moattari A R. (Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor 48109.) Acta oncologica (Stockholm, Sweden), (1989) 28 (3) 389-402. Ref: 78. Journal code: 8709065. ISSN: 0284-186X. Pub. country: Sweden. Language: English.

AB A **review** is given on the clinical features of carcinoid syndrome including symptomatology, diagnostics, biochemistry and treatment. We have reviewed the literature on current therapy of carcinoid patients with special emphasis on the use of the **somatostatin analogue** SMS 20-1995. In addition, we present data on the effects of SMS 201-995 on indices of a clinical, biochemical and tumor growth. **Diarrhea** is abolished or significantly reduced in 75% of patients, flushing improves in 100%, wheezing in 100% with a decrease in airways resistance, and in one patient myopathy has improved. Blood serotonin is notoriously resistant to intervention and urinary 5-HIAA will decrease in 75% of causes but subsequently rebounds in 38%. Tumors, in general, continue to grow, but this may be slowed or in rare cases tumor growth is arrested. In individual instances the tumor may even infarct, leading to spontaneous cure. Tumors secreting PP, ACTH and calcitonin may be particularly resistant to treatment, whereas VIP secreting tumors appear to be sensitive.

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     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 13:43:44 ON 17 NOV 2004
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L2       5075530 S ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR
L3       1349552 S L1 AND L2
L4         94956 S SOMATOSTATIN OR SST
L5         26064 S L4 AND L2
L6       5979652 S ?AGONIST? OR LIGAND? OR INHIBITOR? OR MODULATOR? OR REGULATOR
L7         38217 S L6 AND L4
L8        173209 S DIARRHEA? OR INTRACTABLE () DIARRHEA?
L9          1037 S L8 AND L7
L10          197 S L9 AND REVIEW

=> s diabetic? () complication?
L11         9308 DIABETIC? (W) COMPLICATION?

=> s l11 and l7
L12           24 L11 AND L7

=> s l12 and review
L13            6 L12 AND REVIEW

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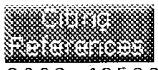

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2003:435886   Document No. 139:128127  Use of somatostatin receptor ligands
     in obesity and diabetic complications.  Boehm, Bernhard O.; Lustig,
     Robert H. (Division of Endocrinology, Ulm University, Ulm/Donau, 89070,
     Germany).  Best Practice & Research, Clinical Gastroenterology, 16(3),
     493-509 (English) 2002.  CODEN: BPRCB6.  Publisher: Bailliere Tindall.
AB   A review.  Somatostatin (SMS) is a potent inhibitory mol.  It
     inhibits both exocrine and endocrine secretory functions of the pancreas,
     suppresses growth hormone secretion and reduces the level of insulin-like
     growth factor-I.  Long-acting somatostatin analogs were currently
     investigated for potential clin. benefits in two settings: (a) control of
     hyperinsulinemia in obesity and (b) control of an excess of pro-angiogenic
     factors in diabetes-assocd. retinal complications.  In two randomized,
     controlled trials the long-acting somatostatin analog octreotide
     retarded progression of the microvascular complications in
     pre-proliferative and advanced stages of diabetic retinopathy.  Inhibition
     of the early phase of insulin secretion by use of octreotide in patients
     with hypothalamic obesity resulted in wt. loss and improved quality of
     life.  Efficacy of octreotide correlated to residual β-cell activity
     prior to the treatment.  Obesity and diabetes mellitus are the most common
     chronic metabolic disorders in the world.  The use of somatostatin
     analogs addressing the various hormonal imbalances of these disorders
     may provide a novel concept for their pharmacol. treatment.

L13  ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2004 ACS on STN
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2001:706663   Document No. 136:129100  Treatment of diabetic retinopathy with
     long-acting somatostatin analogues.  Boehm, B. O.; Feldmann, B.; Lang,
     G. K.; Lang, G. E. (Universitatsklinikum Ulm, Sektion Endokrinologie, and
     Augenklinik, Ulm/Donau, D-89070, Germany).  Octreotide: The Next Decade,
     [Proceedings of a Symposium], Sintra, Portugal, Mar., 1999, 241-257.
     Editor(s): Lamberts, S. W. J.  BioScientifica Ltd.: Bristol, UK. (English)
     1999.  CODEN: 69BVYR.
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AB A **review** discusses the prevalence of diabetes mellitus and the natural course of diabetic retinopathy. The important roles of growth hormone and other growth factors for the development of proliferative retinopathy and their modification by **somatostatin** and its **analogs** are also discussed as a novel basis for the intervention strategies in proliferative diabetic retinopathy. The evidence for the important role of hyperglycemia as the major risk factor for the development of this specific **diabetic complication** is presented.

L13 ANSWER 3 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

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2003518641 EMBASE Use of **somatostatin** receptor **ligands** in obesity and **diabetic complications**. Boehm B.O.; Lustig R.H.. Prof. B.O. Boehm, Division of Endocrinology, Ulm University, Robert-Koch-Strasse 8, 89070 Ulm/Donau, Germany. Bailliere's Best Practice and Research in Clinical Gastroenterology 16/3 (493-509) 2002.
Refs: 104.
ISSN: 1521-6918. CODEN: BBPGFG.
Publisher Ident.: S 1521-6918(02)90320-3. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB **Somatostatin** (SMS) is a potent **inhibitory** molecule. It inhibits both exocrine and endocrine secretory functions of the pancreas, suppresses growth hormone secretion and reduces the level of insulin-like growth factor-1. Long-acting **somatostatin analogues** were currently investigated for potential clinical benefits in two settings: (a) control of hyperinsulinaemia in obesity and (b) control of an excess of pro-angiogenic factors in diabetes-associated retinal complications. In two randomized, controlled trials the long-acting **somatostatin analogue** octreotide retarded progression of the microvascular complications in pre-proliferative and advanced stages of diabetic retinopathy. Inhibition of the early phase of insulin secretion by use of octreotide in patients with hypothalamic obesity resulted in weight loss and improved quality of life. Efficacy of octreotide correlated to residual β-cell activity prior to the treatment. Obesity and diabetes mellitus are the most common chronic metabolic disorders in the world. The use of **somatostatin analogues** addressing the various hormonal imbalances of these disorders may provide a novel concept for their pharmacological treatment.

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97010816 EMBASE Document No.: 1997010816. Streptozotocin-induced ketoacidosis and non-ketonuric diabetes in the rat: Useful models for drug action. Thompson C.S.; Mikhailidis D.P.. C.S. Thompson, Dept. Chem. Pathol./Human Metabolism, Royal Free Hosp. Sch. of Medicine, University of London, Pond Street, London NW3 2QG, United Kingdom. Journal of Pharmaceutical Medicine 6/1-2 (57-85) 1996.
ISSN: 0958-0581. CODEN: JPMDE7. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Diabetes mellitus (DM) is a very common disease associated with a considerable number of complications involving the vascular, renal, nervous and gastrointestinal systems. These problems have been attributed to the complex metabolic changes that are associated with this disease. DM is an inherently difficult disease to study in humans because of the considerable variability of each patient, (e.g. duration of disease, diet, smoking, quality of diabetic control). Although animal models have their

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limitations, they provide a reproducible form of the disease with access to a variety of tissues. This allows an improved analysis of the underlying pathological processes. The present **review** considers several **'diabetic complications'** occurring in the ketoacidotic and non-ketonuric streptozotocin-induced diabetic rat. We have related these changes (e.g. clinical biochemical variables) to the human disease, emphasizing the usefulness of these models in assessing drug action.

L13 ANSWER 5 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN

94343106 EMBASE Document No.: 1994343106. Pancreas-kidney transplantation for intensivists: Perioperative care and complications. Fabrega A.J.; Rivas P.A.; Pollak R.. Division of Transplantation, Department of Surgery, University of Illinois,Chicago, IL 60680, United States. Journal of Intensive Care Medicine 9/6 (281-289) 1994.
ISSN: 0885-0666. CODEN: JICME3. Pub. Country: United States. Language: English. Summary Language: English.

AB Simultaneous pancreas-kidney transplantation is a therapeutic option for type I diabetics with end-stage renal disease. It aims to correct the uremic state, to normalize glucose hemeostasis, and to ameliorate **diabetic complications**. Careful donor-recipient selection and meticulous intra- operative and postoperative care will substantially impact recipient morbidity. An understanding of the technical aspects of the surgical procedure and its metabolic and immunological consequences is necessary to successfully manage a pancreas-kidney transplant recipient, many of whom are nursed in intensive care units. A successful outcome is predicted in early recognition of technical complications and aggressive management of rejection to achieve the current 1-year graft survival rates of 75% for pancreas transplants and 84% for kidney transplants.

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on STN

89184653 EMBASE Document No.: 1989184653. **Regulatory** peptides, the hypothalamus and diabetes. Williams G.; Bloom S.R.. Department of Medicine, University of Liverpool, Liverpool L69 3BX, United Kingdom. Diabetic Medicine 6/6 (472-485) 1989.
ISSN: 0742-3071. CODEN: DIMEEV. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB **Regulatory** peptides are attracting attention in several areas of diabetes research, including the regulation of islet cell secretion, the control of energy balance and blood glucose homeostasis by the hypothalamus, and the pathogenesis of **diabetic complications** such as neuropathy and retinopathy. Hypothalamic **regulatory** peptides are of considerable interest in diabetes, as they may mediate the many neuroendocrine abnormalities of the disease, which in turn may provide clues as to the normal functions of these peptides. This **review** will discuss in general terms the metabolic and neuroendocrine effects of hypothalamic peptides, and then describe in detail the possible importance in diabetes of two specific peptides, **somatostatin** and neuropeptide Y.

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L7        38217 S L6 AND L4
L8       173209 S DIARRHEA? OR INTRACTABLE () DIARRHEA?
L9         1037 S L8 AND L7
L10         197 S L9 AND REVIEW
L11        9308 S DIABETIC? () COMPLICATION?
L12          24 S L11 AND L7
L13           6 S L12 AND REVIEW

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L16          65 L15 AND REVIEW

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L16  ANSWER 1 OF 65     MEDLINE on STN
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1998215372.     PubMed ID: 9556085.   Hormonal regulation of appetite and food
      intake. Hirschberg A L. (Department of Obstetrics and Gynecology,
      Karolinska Hospital, Stockholm, Sweden. ) Annals of medicine, (1998 Feb)
      30 (1) 7-20.  Ref: 135. Journal code: 8906388. ISSN: 0785-3890. Pub.
      country: ENGLAND: United Kingdom. Language: English.
AB    Several clinical disorders are strongly influenced by hormones involved in
      appetite and weight regulation.  Obesity and eating disorders are of
      major importance, because they are associated with severe morbidity and
      considered to be among the greatest health problems in the Western world
      today.  This review describes recent findings in hormonal regulation of
      food intake by substances acting both centrally, such as
      corticotropin-releasing factor, neuropeptide Y and leptin, and
      peripherally, such as cholecystokinin and somatostatin.  Sex hormones
      and glucocorticoids play an important role in long-term regulation of
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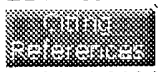
metabolism. The role of these hormones in appetite and weight changes during life as well as during pregnancy and lactation is discussed. Furthermore, the development of **obesity** and eating disorders is influenced, in particular, by steroid hormones. Treatment with sex hormones, as in hormone replacement therapy, affects appetite and weight and may have beneficial effects in preventing android **obesity**. Currently, there is great effort in developing endogenous neurohumoral substances into effective drugs for the treatment of **obesity** and eating disorders. Leptin and neuropeptide Y **analogues** are of interest as potential antiobesity agents.

L16 ANSWER 2 OF 65 MEDLINE on STN



1998126429. PubMed ID: 9465289. Growth hormone-releasing peptides and their **analogs**. Camanni F; Ghigo E; Arvat E. (Department of Internal Medicine, University of Turin, Italy.) Frontiers in neuroendocrinology, (1998 Jan) 19 (1) 47-72. Ref: 172. Journal code: 7513292. ISSN: 0091-3022. Pub. country: United States. Language: English.

AB Growth hormone-releasing peptides (GHRPs) are a series of hepta (GHRP-1)- and hexapeptides (GHRP-2, GHRP-6, Hexarelin) that have been shown to be effective releasers of GH in animals and humans. More recently, a series of nonpeptidyl GH secretagogues (L-692,429, L-692,585, MK-0677) were discovered using GHRP-6 as a template. Some cyclic peptides as well as penta-, tetra-, and pseudotripeptides have also been described. This **review** summarizes recent developments in our understanding of the GHRPs, as well as the current nonpeptide pharmacologic **analogs**. GHRPs and their **analogs** have no structural homology with GHRH and act via specific receptors present at either the pituitary or the hypothalamic level. The GHRP receptor has recently been cloned and it does not show sequence homology with other G-protein-coupled receptors known so far. This evidence strongly suggests the existence of a natural GHRP-like **ligand** which, however, has not yet been found. Although the exact mechanism of action of GHRPs has not been fully established, there is probably a dual site of action on both the pituitary and the hypothalamus, possibly involving **regulatory** factors in addition to GHRH and **somatostatin**. Moreover, the possibility that GHRPs act via an unknown hypothalamic factor (U factor) is still open. The marked GH-releasing activity of GHRPs is reproducible and dose-related after intravenous, subcutaneous, intranasal, and even oral administration. The GH-releasing effect of GHRPs is the same in both sexes, but undergoes age-related variations. It increases from birth to puberty and decreases in aging. The GH-releasing activity of GHRPs is synergistic with that of GHRH and not affected by opioid receptor **antagonists**, while it is only blunted by **inhibitory** influences that are known to nearly abolish the effect of GHRH, such as neurotransmitters, glucose, free fatty acids, glucocorticoids, rhGH, and even exogenous **somatostatin**. GHRPs maintain their GH-releasing effect in somatotrope hypersecretory states, such as acromegaly, anorexia nervosa, and hyperthyroidism. On the other hand, GHRPs and their **analogs** have been reported to be effective in idiopathic short stature, in some situations of GH deficiency, in **obesity**, and in hypothyroidism, while in patients with pituitary stalk disconnection and in Cushing's syndrome the somatotrope responsiveness to GHRPs is almost absent. A potential role in the treatment of short stature, aging, catabolic states, and dilated cardiomyopathy has been envisaged.

L16 ANSWER 3 OF 65 MEDLINE on STN

97239855. PubMed ID: 9085516. Physiological regulation of the human growth

hormone (GH)-insulin-like growth factor type I (IGF-I) axis: predominant impact of age, **obesity**, gonadal function, and sleep. Veldhuis J D; Iranmanesh A. (Department of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, USA.) Sleep, (1996 Dec) 19 (10 Suppl) S221-4. Ref: 17. Journal code: 7809084. ISSN: 0161-8105. Pub. country: United States. Language: English.

AB The growth hormone (GH)-insulin-like growth factor type I (IGF-I) axis is subject to exquisite regulation by multiple internal physiological variables and external cues. This **review** and update summarizes the impact of age, **obesity**, gonadal function and sleep on the control of GH secretion by the pituitary gland, as regulated by the dominant hypothalamic **regulatory** peptides, GH-releasing hormone (GHRH) and **somatostatin**. Available studies show an exponential decline in the calculated daily GH-secretion rate as a function of age in healthy men, such that every 7 years of advancing age beyond age 18-21 results in an approximately 50% decline. There are also strongly negative correlations between the daily GH-secretion rate and indices of **obesity**, such as the body mass index (BMI). For each increase in BMI of 1.5 kg/m2, there is a 50% decrease in the amount of GH secreted per day. At puberty, and across a span of adult ages, gonadal steroid-hormone concentrations in blood positively determine GH release. In particular, serum estradiol and testosterone concentrations are proportionate to GH-secretory burst mass and mean serum GH concentrations. Deep sleep (stages 3 and 4) is accompanied by markedly increased pulsatile GH secretion that can be accounted for mechanistically by presumptive **somatostatin** withdrawal combined with hypothalamic GHRH release. Lastly, body composition (especially visceral adiposity) appears to be a dominant negative determinant of GH production, since the relationships between GH secretion and age, testosterone, or sleep are all attenuated or abolished by adiposity. Recent data using pulsatile GHRH treatment or pharmacological methods to reduce **somatostatin** secretion point to combined defects in GHRH release and **somatostatin** excess as the most plausible pathophysiology of hyposomatotropism accompanying **obesity**.

L16 ANSWER 4 OF 65 MEDLINE on STN

Citing References

84075191. PubMed ID: 6139917. [Peptide hormones of the digestive organs (**review** of the literature)]. Peptidnye gormony organov pishchevareniia (obzor literatury). Germaniuk Ia L. Vrachebnoe delo, (1983 Oct) (10) 74-9. Ref: 24. Journal code: 0413607. ISSN: 0049-6804. Pub. country: USSR. Language: Russian.

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Citing References

2003:569470 Document No.: PREV200300562593. Ghrelin for the gastroenterologist: History and potential. Murray, Charles D. R.; Kamm, Michael A.; Bloom, Stephen R.; Emmanuel, Anton V. [Reprint Author]. Physiology Unit, St. Mark's Hospital, Watford Road, Harrow, HA1 3UJ, UK. a.emmanuel@ic.ac.uk. Gastroenterology, (November 2003) Vol. 125, No. 5, pp. 1492-1502. print.
CODEN: GASTAB. ISSN: 0016-5085. Language: English.

AB Ghrelin, a novel 28-amino acid orexigenic peptide discovered in 1999, has given us further insights into the control of energy homeostasis and growth hormone secretion. As a natural endogenous **ligand** of the growth hormone secretagogue receptor, it potently stimulates growth hormone release but is also implicated in many other homeostatic mechanisms. Released from the stomach, it stimulates lactotroph and corticotroph

secretion, increases appetite and adiposity, has beneficial hemodynamic effects, has prokinetic and gastric acid secretory functions in the stomach, and may even be implicated in sleep. As advances in the understanding of appetite and **obesity** are made, it is timely to **review** the possibly central role of ghrelin in these physiological and pathophysiological states. This **review** will discuss the recent literature concerning this exciting novel neuropeptide and discuss the possible therapeutic possibilities it may open up to us.

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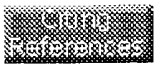

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1998:231981 Document No.: PREV199800231981. Hormonal regulation of appetite and food intake. Hirschberg, Angelica Linden [Reprint author]. Dep. Women Child Health, Div. Obstet. Gynecol., Karolinska Hosp., PO Box 140, S-171 76 Stockholm, Sweden. Annals of Medicine, (Feb., 1998) Vol. 30, No. 1, pp. 7-20. print.
CODEN: ANMDEU. ISSN: 0785-3890. Language: English.

AB Several clinical disorders are strongly influenced by hormones involved in appetite and weight regulation. **Obesity** and eating disorders are of major importance, because they are associated with severe morbidity and considered to be among the greatest health problems in the Western world today. This **review** describes recent findings in hormonal regulation of food intake by substances acting both centrally, such as corticotropin-releasing factor, neuropeptide Y and leptin, and peripherally, such as cholecystokinin and **somatostatin**. Sex hormones and glucocorticoids play an important role in long-term regulation of metabolism. The role of these hormones in appetite and weight changes during life as well as during pregnancy and lactation is discussed. Furthermore, the development of **obesity** and eating disorders is influenced, in particular, by steroid hormones. Treatment with sex hormones, as in hormone replacement therapy, affects appetite and weight and may have beneficial effects in preventing android **obesity**. Currently, there is great effort in developing endogenous neurohumoral substances into effective drugs for the treatment of **obesity** and eating disorders. Leptin and neuropeptide Y **analogues** are of interest as potential antiobesity agents.

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1997:202250 Document No.: PREV199799501453. Physiological regulation of the human growth hormone (GH)-insulin-like growth factor type I (IGF-I) axis: Predominant impact of age, **obesity**, gonadal function, and sleep. Veldhuis, Johannes D. [Reprint author]; Iranmanesh, Ali. Div. Endocrinol. and Metabolism, Dep. Intern. Med., Univ. Va. Health Sci. Cent., Charlottesville, VA 22908, USA. Sleep (Rochester), (1996) Vol. 19, No. 10 SUPPL., pp. S221-S224.
CODEN: SLEED6. ISSN: 0161-8105. Language: English.

AB The growth hormone (GH)-insulin-like growth factor type I (IGF-1) axis is subject to exquisite regulation by multiple internal physiological variables and external cues. This **review** and update summarizes the impact of age, **obesity**, gonadal function, and sleep on the control of GH secretion by the pituitary gland, as regulated by the dominant hypothalamic **regulatory** peptides, GH-releasing hormone (GHRH) and **somatostatin**. Available studies show an exponential decline in the calculated daily GH-secretion rate as a function of age in healthy men, such that every 7 years of advancing age beyond age 18-21 results in an

approximately 50% decline. There are also strongly negative correlations between the daily GH-secretion rate and indices of **obesity**, such as the body mass index (BMI). For each increase in BMI of 1.5 kg/m-2, there is a 50% decrease in the amount of GH secreted per day. At puberty, and across a span of adult ages, gonadal steroid-hormone concentrations in blood positively determine GH release. In particular, serum estradiol and testosterone concentrations are proportionate to GH-secretory burst mass and mean serum GH concentrations. Deep sleep (stages 3 and 4) is accompanied by markedly increased pulsatile GH secretion that can be accounted for mechanistically by presumptive **somatostatin** withdrawal combined with hypothalamic GHRH release. Lastly, body composition (especially visceral adiposity) appears to be a dominant negative determinant of GH production, since the relationships between GH secretion and age, testosterone, or sleep are all attenuated or abolished by adiposity. Recent data using pulsatile GHRH treatment or pharmacological methods to reduce **somatostatin** secretion point to combined defects in GHRH release and **somatostatin** excess as the most plausible pathophysiology of hyposomatotropism accompanying **obesity**.

L16 ANSWER 8 OF 65 CAPLUS COPYRIGHT 2004 ACS on STN

Cushing Reference

2004:954362 New perspectives in the treatment of Cushing's syndrome. Labeur, M.; Arzt, E.; Stalla, G. K.; Paez-Pereda, M. (Dept. of Endocrinology, Max Planck Institute of Psychiatry, Munich, 80804, Germany). Current Drug Targets: Immune, Endocrine and Metabolic Disorders, 4(4), 335-342 (English) 2004. CODEN: CDTIBT. ISSN: 1568-0088. Publisher: Bentham Science Publishers Ltd..

AB Regardless of etiol., all cases of endogenous Cushing's syndrome are due to increased prodn. of cortisol by the adrenal gland. Most are caused by adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas. Alternatively, the glucocorticoid excess may be due to adrenal neoplasia or to ectopic ACTH-secreting tumors. Cushing's syndrome is characterized by endocrine and metabolic alterations such as truncal **obesity**, hypertension, weakness, amenorrhea, hyperglycemia, osteoporosis and depression. Unless treated, the disease is assocd. with high morbidity, and ultimately, mortality. Depending on the etiol. of Cushing's syndrome two different treatment modalities are possible: redn. of pituitary ACTH prodn. or redn. of adrenocortical cortisol secretion. In the absence of efficient drug therapy, transsphenoidal resection of the pituitary adenoma is the primary treatment of choice for the redn. of ACTH secretion. In the last years there was much progress in understanding the mol. mechanisms that control the function of the hypothalamic-pituitary-adrenal axis. Thus, new insights made it possible to identify potential drug targets for the treatment of Cushing's syndrome. The present article **reviews** different drug targets and therapeutic options including drugs that control the central ACTH regulation, e.g. by modulating signaling pathways and transcriptional regulation of ACTH biosynthesis, corticotrophin releasing hormone (CRH) or glucocorticoid receptor **antagonists**, **inhibitors** of glucocorticoid synthesis, ketoconazole, **somatostatin** and dopamine **analogs**. Some of these substances might be useful for the treatment of Cushing's syndrome.

L16 ANSWER 9 OF 65 CAPLUS COPYRIGHT 2004 ACS on STN

Cushing Reference

2004:436701 Document No. 140:399176 Inhibition of insulin secretion as a new drug target in the treatment of metabolic disorders. Bondo Hansen, J.; Arkhammar, Per O. G.; Bodvarsdottir, Thora B.; Wahl, Philip (Discovery, Novo Nordisk A/S, Malov, DK 2760, Den.). Current Medicinal Chemistry,

11(12), 1595-1615 (English) 2004. CODEN: CMCHE7. ISSN: 0929-8673. Publisher: Bentham Science Publishers Ltd..

AB A **review**. The pattern of insulin release is crucial for regulation of glucose and lipid hemostasis. Deficient insulin release causes hyperglycemia and diabetes, whereas excessive insulin release can give rise to serious metabolic disorders, such as nesidioblastosis (Persistent Hyperinsulinemic Hypoglycemia of Infancy, PHHI) and might also be closely assocd. with development of type 2 diabetes and **obesity**. Type 2 diabetes is characterized by fasting hyperinsulinemia, insulin resistance, and impaired insulin release, i.e. reduced 1st phase insulin release and decreased insulin pulse mass. The beta cell function of patients with type 2 diabetes slowly declines and will ultimately result in beta cell failure and increasing degrees of hyperglycemia. Type 2 diabetes, in combination with **obesity** and cardiovascular disorders, forms the metabolic syndrome. It was possible to improve beta cell function and viability in preclin. models of type 1 and type 2 diabetes by reducing insulin secretion to induce beta cell rest. Clin. studies have furthermore indicated that **inhibitors** of insulin release will be of benefit in treatment or prevention of diabetes and **obesity**. Pancreatic beta cells secrete insulin in response to increased metab. and by stimulation of different receptors. The energy status of the beta cell controls insulin release via regulation of open probability of the ATP sensitive potassium (KATP) channels to affect membrane potential and the intracellular Ca concn. [Ca2+]i. Other membrane bound receptors and ion channels and intracellular targets that modulate [Ca2+]i will affect insulin release. Thus, insulin release is regulated by e.g. **somatostatin** receptors, GLP-1 receptors, muscarinic receptors, cholecystokinin receptors, and adrenergic receptors. Although the relationship between hyperinsulinemia and certain metabolic diseases was known for decades, only a few **inhibitors** of insulin release were characterized in vitro and in vivo. These include the KATP channel openers diazoxide and NN414 and the **somatostatin** receptor **agonist** octreotide.

L16 ANSWER 10 OF 65 CAPLUS COPYRIGHT 2004 ACS on STN

Online References

2003:885950 Document No. 140:105425 Ghrelin and the endocrine pancreas. Broglio, Fabio; Gottero, Cristina; Benso, Andrea; Prodam, Flavia; Volante, Marco; Destefanis, Silvia; Gauna, Carlotta; Muccioli, Giampiero; Papotti, Mauro; van der Lely, Aart Jan; Ghigo, Ezio (Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Turin, Italy). Endocrine, 22(1), 19-24 (English) 2003. CODEN: EOCRE5. ISSN: 1355-008X. Publisher: Humana Press Inc..

AB A **review**. Ghrelin is a 28-amino-acid peptide predominantly produced by the stomach, while substantially lower amts. derive from other tissues including the pancreas. It is a natural **ligand** of the GH secretagogue (GHS) receptor (GHS-R1a) and strongly stimulates GH secretion, but acylation in serine 3 is needed for its activity. Ghrelin also possesses other endocrine and non-endocrine actions reflecting central and peripheral GHS-R distribution including the pancreas. The wide spectrum of ghrelin activities includes orexigenic effect, control of energy expenditure, and peripheral gastroenteropancreatic actions. Circulating ghrelin levels mostly reflect gastric secretion as indicated by evidence that they are reduced by 80% after gastrectomy and even after gastric bypass surgery. Ghrelin secretion is increased in anorexia and cachexia but reduced in **obesity**, a notable exception being Prader-Willi syndrome. The neg. assocn. between ghrelin secretion and body wt. is emphasized by evidence that wt. increase and decrease reduces and augments circulating ghrelin levels in anorexia and **obesity**, resp., and agrees with the clear

neg. assocn. between ghrelin and insulin levels. In fact, ghrelin secretion is increased by fasting whereas it is decreased by glucose load as well as during euglycemic clamp but not after arginine or free fatty acid load in normal subjects; in physiol. conditions, however, the most remarkable **inhibitory** input on ghrelin secretion is represented by **somatostatin** as well as by its natural **analog** cortistatin that concomitantly reduce β-cell secretion. This evidence indicates that the endocrine pancreas plays a role in directly or indirectly modulating ghrelin secretion. As anticipated, ghrelin, in turn, is expressed within the endocrine pancreas, although it is still matter of debate if it is expressed by β-, α-, or non-α/non-β cells.
Moreover, GHS-R1a expression in the pancreas has been demonstrated by many authors. Some impact of synthetic GHS on insulin secretion and glucose metab. had been reported in both animal and human studies. Depending on dose and exptl. conditions ghrelin has been shown able to inhibit or stimulate insulin secretion in animals. In humans, ghrelin administration is followed by transient inhibition of insulin levels that surprisingly follows persistent increase in plasma glucose levels suggesting that ghrelin would also directly or indirectly activate glycogenolysis. Current studies indicate that ghrelin also blunts the insulin response to arginine but not that to oral glucose load in humans. These acute effects of ghrelin are independent of any cholinergic mediation and are not shared by synthetic, peptidyl GHS indicating they are likely mediated by a non-GHS-R1a receptor. These acute effects of ghrelin on insulin secretion would be short-lasting, and it has to be remembered that long-term treatment with synthetic non peptidyl GHS in healthy elderly subjects was followed by insulin resistance. In all, it is already clear that ghrelin has remarkable impact in modulating insulin secretion and glucose metab. Insulin and ghrelin secretions seem linked by a neg. functional relationship that strengthens the hypothesized role of ghrelin in participating in the management of the neuroendocrine and metabolic response to variations in energy balance.

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